theguardian

Gut bacteria regulate nerve fibre insulation

Research suggests that gut bacteria may directly affect brain structure and function, offering new ways to treat multiple sclerosis and psychiatric conditions

Mo Costandi

Tuesday 5 April 2016 10.00 EDT

Far from being silent partners that merely help to digest food, the bacteria in your gut may also be exerting subtle influences on your thoughts, moods, and behaviour. And according to a new study from researchers at University College Cork, your gut microbes might affect the structure and function of the brain in a more direct way, by regulating myelination, the process by which nerve fibres are insulated so that they can conduct impulses properly.

The surprising new findings, published today in the journal *Translational Psychiatry*, provide what is perhaps the strongest evidence yet that gut bacteria can have a direct physical effect on the brain, and suggest that it may one day be possible to treat debilitating demyelinating diseases such as multiple sclerosis, and even psychiatric disorders, by altering the composition of the gut's microbial menagerie in some way or another.

Gut microbe research has exploded in the past 10 years, and in that time, it has become increasingly clear that there is a two-way line of communication between gut bacteria and the brain. The human gut microbiome seems to play important roles in health and disease, and alterations in its composition have been implicated in a wide range of neurological and psychiatric conditions, including autism, chronic pain, depression, and Parkinson's Disease, although the links still remain somewhat tenuous.

John Cryan and Gerard Clarke of the APC Microbiome Institute are particularly interested in how gut bacteria might influence the brain structures involved in anxiety-like behaviours. Last year, they published evidence that germ-free mice, which are completely devoid of gut bacteria, exhibit altered gene expression in the amygdala, a small, almond-shaped brain structure that is critical regulating emotions and social behaviour. The animals were reared in highly sterile conditions, so that bacteria cannot colonise their guts after birth - as a result certain genes involved in neuronal function appear to more active in their brains compared to those of normal mice.

Following up on these earlier findings, Cryan and Clarke decided to systematically analyse how gut microbes might affect the activity of genes in other parts of the brain. In their latest study, which was led by Ph.D. student Alan Hoban, the researchers used RNA sequencing technology to examine gene expression in the prefrontal cortex, which plays a key role in executive functions such as planning and decision-making, and also in processing emotional information, by exercising 'top-down' control over the amygdala and other sub-cortical brain structures.

Using the same approach taken in their previous study, the researchers compared gene expression levels in the germ-free mice to that seen in normal animals. They identified approximately 90 genes that are differentially expressed in the germ-free animals and, to their surprise, they found that a handful of them are well known to be involved in myelination, and appear to be far more active in the prefrontal cortex of germ-free mice compared to that of normal animals. Some of the genes they identified encode proteins that form structural components of myelin, while others play a regulatory role in myelin formation.

Intrigued by their results, the researchers went on to dissect the animals' brains, and used an electron microscope to examine tissue from the prefrontal cortex closely. This revealed that the differences in gene expression were associated with observable anatomical differences, with nerve fibres in the prefrontal cortex of the germ-free animals having thicker myelin sheaths than those in the normal animals.

Importantly, the researchers found that these effects were far bigger in male mice than than in females, and that they could be partly reversed by introducing gut bacteria into the germ-free mice after they had been weaned.

Myelin is a fatty substance which wraps itself around nerve fibres, preventing leakage of electrical current and facilitating the conductance of nervous impulse. In the brain, it is produced by specialised glial cells called oligodendrocytes, each of which has a small

number of branches that form a flat sheet of myelin and wrap around a short segment of an axon. Individual axonal fibres are therefore ensheathed by short segments of myelin from many different oligodendrocytes. When a nerve cell fires, its electrical impulses jump between the gaps in the myelin sheath, and this hastens their propagation along the length of the fibre.

The process of myelination, by which myelin is formed and laid down around axons, is crucial for development and maturation of the brain. During adolescence, the brain undergoes a protracted period of heightened neural plasticity, during which large numbers of synapses are eliminated in the prefrontal cortex, and a wave of myelination sweeps across this part of the brain. These processes refine the circuitry in the prefrontal cortex, and increase its connectivity to other brain regions. The increased plasticity make adolescents more susceptible to risky behaviour and mental health conditions such as schizophrenia, however.

Myelination is also critical for normal, everyday functioning of the brain. Myelin increases a nerve fibre's conduction velocity by up to a hundred times, and so when it breaks down, the consequences can be devastating. In multiple sclerosis, for example, break down of myelin in the brain and spinal cord can lead to difficulty with vision and movement, and in severe cases to complete blindness and paralysis.

"We've unlocked a process that puts the brakes on myelin formation in the prefrontal cortex," says Cryan, "and to our knowledge this is the first study showing a clear relationship between the microbiome and myelination in the brain." The new findings could, therefore, eventually lead to novel treatments for multiple sclerosis and other demyelinating diseases, based on prebiotics, probiotics, or even fecal transplants, all of which could potentially be used to adjust the exact composition of microbes in the gut.

The results have wider implications, though. There is growing evidence that the distribution of myelin in the brain can be modified in response to experience, and Cryan points to a 2012 study showing that social isolation impairs myelination in the prefrontal cortex of adult mice. The new findings therefore offer tantalizing clues about how gut bacteria might regulate brain plasticity in response to isolation and other social factors or environmental stimuli.

Other recent work shows that gut microbes control the maturation and function of microglia, the immune cells that eliminate unwanted synapses in the brain; it is, therefore, tempting to speculate that age-related changes to gut microbe composition might regulate myelination and synaptic pruning in adolescence and could, therefore, contribute to cognitive development. Learning more about the relationship between gut microbes and the brain could therefore help researchers to understand the brain changes that occur during adolescence.

"This is an exciting new paper [which marks] an important step forward in research on the gut-brain axis," says microbiologist Elisabeth Bik of Stanford University. "Although we have to be careful in extrapolating the findings to humans, it provides convincing

evidence for the complex communication between gut microbes and the brain, and supports the hypothesis that… gut microbes regulate not only anatomical structure, but probably behaviour and mood as well."

Cryan says his team is now performing similar experiments in mice of different ages, to try and determine the stages of development at which gut microbes might exert such effects, and hopes that other researchers will use microelectrodes to investigate any functional consequences of myelination regulation by gut bacteria. "We also want to understand the underlying mechanism. What's in the microbiome that's driving this? Is it due to some metabolite or, more likely, the absence of some metabolite, and could we recapitulate it with antibiotics, for example?"

Reference

Hoban, A. E., *et al*. (2016). Regulation of prefrontal cortex myelination by the microbiota. *Transl. Psychiatry*, DOI: 10.1038/tp.2016.42 [Full text]

Topics

Neuroscience